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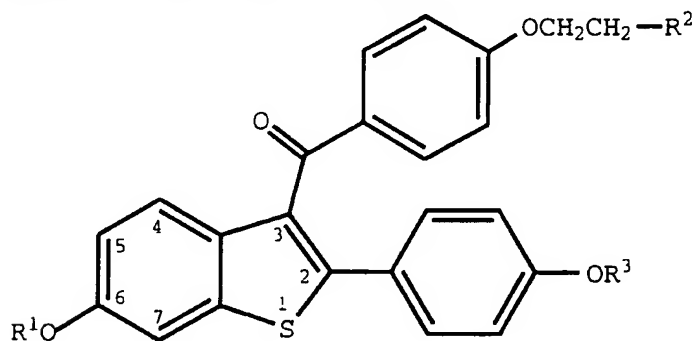
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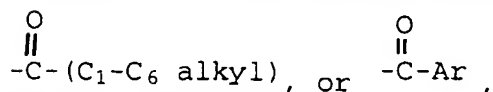
(54) **Inhibition of vasomotor symptoms and treatment of psychological disturbances surrounding post-menopausal syndrome.**

(57) A method of inhibiting vasomotor symptoms and attending psychological disturbances surrounding post-menopausal syndrome comprising administering to a female human in need of treatment an effective amount of a compound having the formula



(I)

wherein R<sup>1</sup> and R<sup>3</sup> are independently hydrogen, -CH<sub>3</sub>,



wherein Ar is optionally substituted phenyl;

R<sup>2</sup> is selected from the group consisting of pyrrolidin, hexamethylen amino, and piperidino; or a pharmaceutically acceptable salt or solvate thereof.

It has been noted throughout human history that women, upon reaching the age of menopause, have suffered from a variety of symptoms associated with the decline in ovarian function. Although the etiology of these symptoms is not clearly understood, it appears to be linked with the decline and imbalance of natural hormones, particularly the sex related hormones and more particularly to the decrease in the production of estrogens. Many symptoms have been linked to what is generally called, "the post-menopausal syndrome". These symptoms are often highly idiosyncratic and of varying severity and length of duration both between different patients as well as within the same patient. Many of the symptoms are serious and sometimes life-threatening pathologies, e.g., osteoporosis, hyperlipidemia, and type II diabetes. Some symptoms are less serious, but cause a great deal of pain and/or suffering, e.g., hot flashes, palpitations, atrophic vaginitis, joint pain, and muscular weakness. Yet other symptoms are of a psychological nature, e.g., headache, dizziness, lack of concentration, sleeplessness, apathy, lassitude, depression, and a sense of uselessness. The psychological symptoms are probably the most idiosyncratic of all in the post-menopausal syndrome and the least understood. Many have argued that there is no post-menopausal syndrome as a true psychiatric syndrome, but it is undeniable that these are common in post-menopausal women and make their appearance at the onset of menopause. It is not clear whether these psychological symptoms are the direct effect of estrogen deprivation in the central or peripheral nervous system or if the symptoms are the result of the vasomotor effects of estrogen deprivation, e.g., hot flashes which disturb sleep may cause the tiredness and the apathy so often seen.

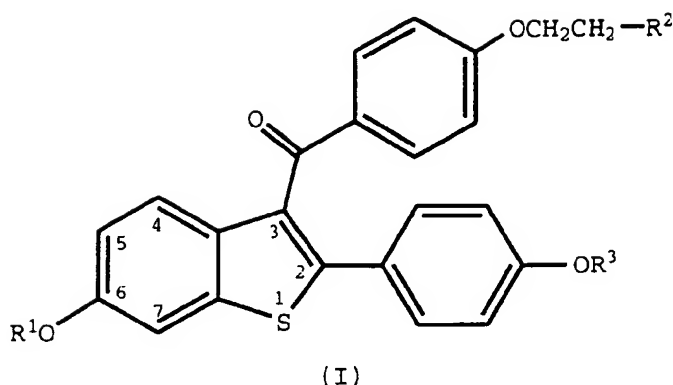
The subject of this invention deals with the treatment of the vasomotor and psychological symptoms associated with menopause. The major and most common vasomotor symptom is hot flashes and/or flushes and the resulting sweats. Hot flashes are embarrassing, uncomfortable, and disturb the ability to sleep. A somewhat less common symptom is the palpitation of the heart rhythm, which although usually not pathological, can be very frightening and a cause of discomfort. The least common vasomotor symptoms are those of joint pain and muscular weakness. Additionally, the treatment of the associated psychological symptoms are the subject of this invention, although it not clear if this treatment is due to a direct impact on the nervous system or an indirect effect of the treatment of the vasomotor abnormalities.

There is currently only one approved method for the treatment of the above mentioned symptoms for post-menopausal women and that is the administration of exogenous estrogens or hormone replacement therapy. Although this therapy is very effective, it does entail some serious liabilities. The most serious liability associated with the administration of estrogens is the threat of endometrial cancer, and as a result, a progestinal agent must be given either along with or serially with the estrogen to reduce this risk. The inclusion of a progestin in a hormone replacement protocol makes such a regimen unattractive to a majority of women due to the progestin's negative psychological side-effects. Additionally, the added progestins can negate some of the positive effects of the estrogens, e.g., the control of hyperlipidemia. Many women do not like other side-effects of a hormone replacement therapy, e.g., the resumption of menses, weight gain, and tenderness of breast tissue. The overall result is that while hormone replacement therapy is effective in treating many of the vasomotor and psychological symptoms associated with the menopause, there is poor patient compliance. Ideally, a better treatment for these symptoms would be useful.

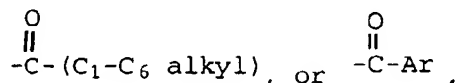
The pharmacological effects of the hormones such as estrogen are poorly understood and often contradictory in many cases, e.g., in endometriosis which is caused by an inappropriate response of certain tissues to estrogen, can in some cases be treated by estrogen administration, yet in others treated by the administration of androgens. It is often unclear what the particular response to a hormone will be in the treatment of a disease and therefore each disease must be investigated on a case by case basis.

The molecular mechanism of how the steroid hormone works is somewhat better understood, in that it is known that the hormone binds to a specific receptor in the cellular cytosol. The hormone-receptor complex is translocated to the nucleus of the target cell where it regulates gene function. Therefore, it can be said that the hormone is a gene regulatory molecule. It is not known exactly which genes are activated or suppressed in the cell or whether the same hormone operates the same way in each target cell. It is probably this lack of knowledge which creates the myriad of surprising and contradictory effects which all hormones display in their pharmacology.

This invention provides methods for inhibiting vasomotor symptoms and attending psychological disturbances surrounding post-menopausal syndrome comprising administering to a female human in need of treatment an effective amount of a compound of formula I



wherein R<sup>1</sup> and R<sup>3</sup> are independently hydrogen, -CH<sub>3</sub>,



wherein Ar is optionally substituted phenyl;

R<sup>2</sup> is selected from the group consisting of pyrrolidino, hexamethyleneimino, and piperidino; and pharmaceutically acceptable salts and solvates thereof.

The current invention concerns the discovery that a select group of 2-phenyl-3-arylbenzothiophenes (benzothiophenes), those of formula I, are useful for inhibiting vasomotor symptoms and attending psychological disturbances surrounding post-menopausal syndrome. The methods of treatment provided by this invention are practiced by administering to a human in need of a dose of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, that is effective to inhibit vasomotor symptoms and attending psychological disturbances surrounding post-menopausal syndrome. The term inhibit is defined to include its generally accepted meaning which includes prophylactically treating a human subject to incurring the characteristics described, and holding in check and/or treating existing characteristics. As such, the present method includes both medical therapeutic and/or prophylactic treatment, as appropriate.

Raloxifene, a compound of this invention wherein it is the hydrochloride salt of a compound of formula 1, R<sup>1</sup> and R<sup>3</sup> are hydrogen and R<sup>2</sup> is 1-piperidinyl, is a nuclear regulatory molecule. Raloxifene has been shown to bind to the estrogen receptor and was originally thought to be a molecule whose function and pharmacology was that of an anti-estrogen in that it blocked the ability of estrogen to activate uterine tissue and estrogen dependent breast cancers. Indeed, raloxifene does block the action of estrogen in some cells; however in other cell types, Raloxifene activates the same genes as estrogen does and displays the same pharmacology, e.g., osteoporosis, hyperlipidemia. As a result, raloxifene has been referred to as an anti-estrogen with mixed agonist-antagonist properties. The unique profile which raloxifene displays and differs from that of estrogen is now thought to be due to the unique activation and/or suppression of various gene functions by the raloxifene-estrogen receptor complex as opposed to the activation and/or suppression of genes by the estrogen-estrogen receptor complex. Therefore, although Raloxifene and estrogen utilize and compete for the same receptor, the pharmacological outcome from gene regulation of the two is not easily predicted and is unique to each.

Generally, the compound is formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated as elixirs or solutions for convenient oral administration, or administered by the intramuscular or intravenous routes. The compounds can be administered transdermally, and may be formulated as sustained release dosage forms and the like.

The compounds used in the methods of the current invention can be made according to established procedures, such as those detailed in U.S. Patent Nos. 4,133,814, 4,418,068, and 4,380,635 all of which are incorporated by reference herein. In general, the process starts with a benzo[b]thiophene having a 6-hydroxyl group and a 2-(4-hydroxyphenyl) group. The starting compound is protected, acylated, and deprotected to form the formula I compounds. Examples of the preparation of such compounds are provided in the U.S. patents discussed above. Substituted phenyl includes phenyl substituted once or twice with C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, hydroxy, nitro, chloro, fluoro, or tri(chloro or fluoro)methyl.

The compounds used in the methods of this invention form pharmaceutically acceptable acid and base

addition salts with a wide variety of organic and inorganic acids and bases and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanoic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate,  $\beta$ -hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, chloride, cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, teraphthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propionate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzene-sulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like. A preferred salt is the hydrochloride salt.

The pharmaceutically acceptable acid addition salts are typically formed by reacting a compound of formula I with an equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethyl ether or benzene. The salt normally precipitates out of solution within about one hour to 10 days and can be isolated by filtration or the solvent can be stripped off by conventional means.

Bases commonly used for formation of salts include ammonium hydroxide and alkali and alkaline earth metal hydroxides, carbonates, as well as aliphatic and primary, secondary and tertiary amines, aliphatic diamines. Bases especially useful in the preparation of addition salts include ammonium hydroxide, potassium carbonate, methylamine, diethylamine, ethylene diamine and cyclohexylamine.

The pharmaceutically acceptable salts generally have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions.

Pharmaceutical formulations can be prepared by procedures known in the art. For example, the compounds can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions, powders, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols.

The compounds can also be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for instance by intramuscular, subcutaneous or intravenous routes. Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

The particular dosage of a compound of formula I required to inhibit vasomotor symptoms and attending psychological disturbances surrounding post-menopausal syndrome, according to this invention will depend upon the severity of the condition, the route of administration, and related factors that will be decided by the attending physician. Generally, accepted and effective daily doses will be from about 0.1 to about 1000 mg/day, and more typically from about 50 to about 200 mg/day. Such dosages will be administered to a subject in need of treatment from once to about three times each day, or more often as needed to effectively treat the symptoms.

It is usually preferred to administer a compound of formula I in the form of an acid addition salt, as is customary in the administration of pharmaceuticals bearing a basic group, such as the piperidino ring. It is also advantageous to administer such a compound by the oral route to an aging human (e.g. a post-menopausal female). For such purposes the following oral dosage forms are available.

## Formulations

In the formulations which follow, "Active ingredient" means a compound of formula I.

**Formulation 1: Gelatin Capsules**

Hard gelatin capsules are prepared using the following:

	Ingredient	Quantity (mg/capsule)
5	Active ingredient	0.1 - 1000
	Starch, NF	0 - 650
	Starch flowable powder	0 - 650
10	Silicone fluid 350 centistokes	0 - 15

The ingredients are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules.

Examples of specific capsule formulations of the compound of formula 1 wherein R<sup>2</sup> is piperidino, (raloxifene), that have been made include those shown below:

**Formulation 2: Raloxifene capsule**

	Ingredient	Quantity (mg/capsule)
20	Raloxifene	1
	Starch, NF	112
	Starch flowable powder	225.3
25	Silicone fluid 350 centistokes	1.7

**Formulation 3: Raloxifene capsule**

	Ingredient	Quantity (mg/capsule)
30	Raloxifene	5
	Starch, NF	108
	Starch flowable powder	225.3
35	Silicone fluid 350 centistokes	1.7

**Formulation 4: Raloxifene capsule**

	Ingredient	Quantity (mg/capsule)
40	Raloxifene	10
	Starch, NF	103
	Starch flowable powder	225.3
45	Silicone fluid 350 centistokes	1.7

**Formulation 5: Raloxifene capsule**

	Ingredient	Quantity (mg/capsule)
50	Raloxifene	50
	Starch, NF	150
55	Starch flowable powder	397
	Silicone fluid 350 centistokes	3.0

The specific formulations above may be changed in compliance with their reasonable variations provided.

A tablet formulation is prepared using the ingredients below:

**Formulation 6: Tablets**

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Ingredient	Quantity (mg/tablet)
Active ingredient	0.1 - 1000
Cellulose, microcrystalline	0 - 650
Silicon dioxide, fumed	0 - 650
Stearate acid	0 - 15

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15 The components are blended and compressed to form tablets.

Alternatively, tablets each containing 0.1 - 1000 mg of active ingredient are made up as follows:

**Formulation 7: Tablets**

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Ingredient	Quantity (mg/tablet)
Active ingredient	0.1 - 1000
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone	4
(as 10% solution in water)	
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

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35 The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

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Suspensions each containing 0.1 - 1000 mg of medicament per 5 mL dose are made as follows:

**Formulation 8: Suspensions**

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Ingredient	Quantity (mg/5 ml)
Active ingredient	0.1 - 1000 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to	5 mL

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The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with some of

the water and added, with stirring. Sufficient water is then added to produce the required volume.

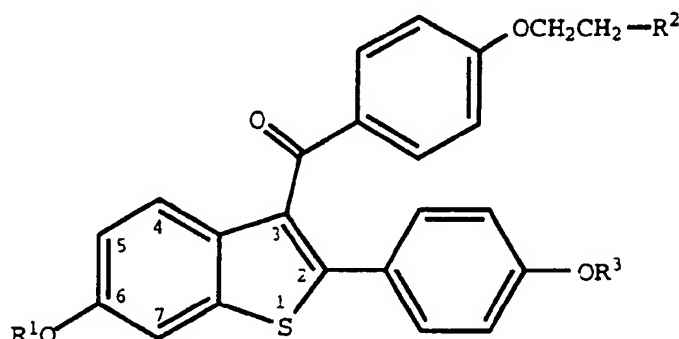
### TEST PROCEDURE

Five to fifty women are selected for the clinical study. The women are post-menopausal, i.e., have ceased menstruating for between 6 and 12 months prior to the study's initiation, are in good general health, and suffer from one or more of the above mentioned vasomotor and/or psychological symptoms. Because of the idiosyncratic and subjective nature of these post-menopausal symptoms, the study has a placebo control group, i.e., the women are divided into two groups, one of which receive the active agent of this invention and the other receive a placebo. Women in the test group receive between 50-200 mg of the drug per day by the oral route. They continue this therapy for 3-12 months. Accurate records are kept as to the number and severity of the above mentioned symptoms in both groups and at the end of the study these results are compared. The results are compared both between members of each group and also the results for each patient are compared to the symptoms reported by each patient before the study began.

Utility of the compounds of the invention is illustrated by the positive impact they have on one or more of the symptoms when used in a study as above.

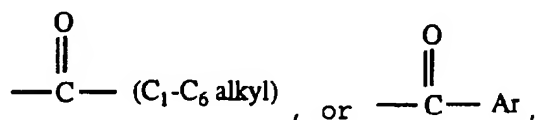
### Claims

1. The use of a compound having the formula



(I)

wherein R¹ and R³ are independently hydrogen, -CH₃,



wherein Ar is optionally substituted phenyl;

R² is selected from the group consisting of pyrrolidino and piperidino; or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament useful for inhibiting vasomotor symptoms and attending psychological disturbances surrounding post-menopausal syndrome.

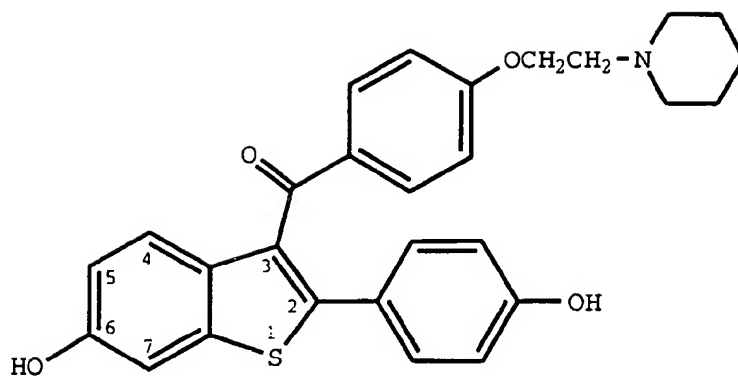
2. The use of Claim 1 wherein said compound is the hydrochloride salt thereof.

3. The use of Claim 1 wherein said medicament is prophylactic.

4. The use of Claim 1 wherein said compound is

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or its hydrochloride salt.

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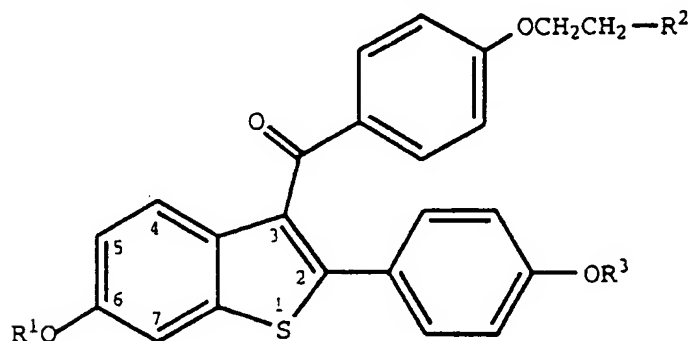
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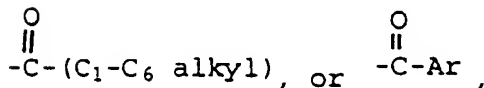
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European Patent  
Office

# EUROPEAN SEARCH REPORT

Application Number  
EP 94 30 9473

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y	EP-A-0 178 862 (BCM TECHNOLOGIES, INC.) * page 13, line 1 - line 22 * * page 1, line 18 - line 29; claims 3,4 * ---	1-4	A61K31/445 A61K31/40 A61K31/38
Y	JOURNAL OF MEDICINAL CHEMISTRY, vol. 27, no. 8, pages 1057-1066, C.D. JONES ET AL. 'ANTIESTROGENS.2.' * page 1057 * ---	1-4	
D,Y	US-A-4 418 068 (JONES) 29 November 1983 * abstract; claims * ---	1-4	
Y	BE-A-678 807 (IMPERIAL CHEMICAL INDUSTRIES) 30 September 1966 * page 6, line 9 - page 7, line 4 * -----	1-4	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
			A61K
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 17 July 1995	Examiner Foerster, W
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document	

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